

REMARKS

Upon entry of the present amendment, claims 1 and 3-19 will be pending. Applicants have cancelled claim 2, amended claims 1, 3, 4, and 6-9, and added new claims 12-19. Support for these amendments and new claims can be found throughout the application as filed, e.g., at page 5, lines 17-24; page 8a, line 21 to page 9a, line 3; page 10, lines 23-27; page 14, line 27, to page 15, line 29; page 16, lines 1-16; page 17, lines 19-25; and the claims as filed, *inter alia*.

In the specification, previously filed pages 8a-10a have been reordered, and certain objected-to phrases have been deleted from those pages, as described further below.

No new matter has been added.

Objections to the Specification

At pages 2-3 of the Office Action mailed December 21, 2006 (the "Office Action"), the Examiner noted that there was an error in the ordering of the replacement pages 8a-10a. As the Examiner suggested, Applicants request that said replacement pages be ordered as set forth above, which restores the logical order of said pages.

Further at pages 3-4, the phrase "for the production of a pharmaceutical composition" was objected to as new matter. While Applicants vehemently do not concur that there is insufficient support for this phrase in the application as filed, Applicants have amended the specification to remove this phrase, which appeared on pages 8a-10a, solely to further prosecution.

In light of these amendments, Applicants request that the objections to the specification be withdrawn.

Claim Objections

At pages 4-5 of the Office Action, claims 9-11 were objected to as being in improper dependent format. Applicants have amended claim 1 to specify that there are mutations in both VAI and VAII genes; claim 9 has been amended to specify a human adenovirus derived from a serotype between 1 and 50, inclusive, that has both a VAI gene and a VAII gene, with genetic

mutations in the VAI gene and the VAII gene. One of skill in the art will appreciate that this excludes any virus between 1 and 50 that does not have both a VAI and VAII gene. Claim 11 recites an adenovirus that is a mutant adenovirus dl331 further comprising a mutation in the VAII RNA gene. Applicants submit that these amendment correct the improper dependency and render claims 9 and 11 further narrowing of claim 1, and therefore request withdrawal of the objections thereto.

Claim Rejections under 35 U.S.C. § 112 - Written Description

Claims 3 and 11 were rejected at pages 5-7 as allegedly lacking in written description support. Applicants respectfully traverse.

Turning first to claim 11, this claim has been amended by Applicants to recite a method using an adenovirus that is a mutant adenovirus dl331 further comprising a mutation in the VAII RNA gene. While there may not be specific mention made of mutating the VAII gene of dl331, Applicants submit that methods which use this virus, which as the examiner notes has a defective VAI gene, are disclosed in the application (see, e.g., Examples 1-3, pages 20-24); the application further discloses methods that uses viruses with defects in both VAI and VAII genes (see the entire application, e.g., page 7, lines 4-7; pages 8a-10; and the claims as filed), and teaches making mutations in both genes (see the entire application, e.g., page 7, lines 4-7; and pages 8a-10). Applicants therefore submit that there is ample support for this claim, and request withdrawal of the rejection thereof.

Regarding claim 3, Applicants have amended this claim to recite methods wherein the adenovirus further has a mutation in the sequences of at least one gene that controls the expression of one or both of the VAI and VAII RNA genes. A number of genes that control expression of the VAI or VAII genes were known in the art at the time of filing, and one of skill in the art would readily be able to identify and select these genes.

For at least these reasons, Applicants submit that the claims as amended have ample written description support in the application as filed, and request withdrawal of the rejection under 35 U.S.C § 112.

Rejections under 35 U.S.C. § 112 -- Enablement

Claims 1-11 were rejected at pages 7-9 of the Office Action as allegedly lacking enabling support in the application as filed. Applicants respectfully traverse.

First, at pages 7-8, claims 1-8 were rejected as allegedly lacking enablement of the full scope of the genus of adenoviruses from any species, not limited to human adenovirus. Applicants note that claim 1 has been amended to recite only those adenoviruses that have both VAI and VAI genes. Applicants submit that this scope is fully and amply enabled, and further recitation of "human" adenovirus is unnecessary. The VAI and VAI genes were identified and indeed well known in the art at the time of filing, so one of skill in the art would readily have been able to identify and select appropriate adenoviruses for use in the claimed methods, without undue experimentation. Applicants have also added new claim 19, which specifies that the adenovirus is human.

The claims were further rejected as lacking enablement for failing to require that the adenovirus replicate selectively in tumor cells, or for failing to specify the type of tumor cells. The Office Action stated at page 8 that "there is no guidance for use of adenovirus for treating cancer where the adenovirus does not replicate in these two types of tumor cells... or will not replicate in tumor cells having a normal ras pathway or that is responsive to interferons." Applicants respectfully traverse.

As a first matter, Applicants have amended claim 1 to specify that the adenovirus can replicate selectively in the cancer cells, and submit that this overcomes the first part of the rejection.

There is no absolute requirement that any claimed method be effective 100% of the time; it is accepted that the presence of inoperative embodiments within a claim, so long as the number is not overwhelming, does not render the claim unpatentable. As noted at page 7, lines 25-27, of the application as filed, "Generally speaking, it is considered that 80% of tumors have an activated Ras pathway." No evidence to the contrary has been introduced. Thus, even if the claimed methods only work in ras-activated cells, the methods will be effective in at least 80% of

cancers, which represents the vast majority of cancers. Thus Applicants submit that the claim is amply enabled over the claimed genus of cancers.

Finally, with regards to claim 4, which was rejected at pages 8-9 of the action, Applicants note that in the parlance of a person of skill in the art, a "gene" is generally considered to include a coding or transcribed region, as well as any regulatory elements including promoters and repressors. Applicants have added new claim 14, which specifies that the mutation in one or more genes in the group of E1a, E1b, and E4 is a mutation in a promoter region. Applicants submit that claim 4 is fully enabled.

For at least these reasons, Applicants submit that the claims as amended are amply enabled.

Rejections under 35 U.S.C. § 112 -- Indefiniteness

Claims 1-11 were further rejected at pages 9-11 as allegedly being indefinite. Applicants respond as follows.

Claim 1 was rejected for allegedly having missing steps; Applicants have amended claim 1 to recite "a subject having cancer," and submit that this remedies the alleged defect.

Claim 4 was rejected as allegedly unclear. Applicants have amended claim 4 to delete the reference to "in the VA RNA genes" and submit that this remedies the alleged defect.

Claim 8 was rejected for use of the phrase "such as;" this phrase has been deleted, as has the language following it. Applicants submit that this remedies the alleged defect.

Claim 9 was rejected as allegedly unclear for recitation of "a human adenovirus derived from a serotype between 1 and 50." While Applicants do not concur that this claim was indefinite as written, Applicants have amended the claim to specify that this range is "inclusive." While there may be no *ipsis verbis* support for this amendment, Applicants submit that this meaning is implicit from general usage and the context of the application (see, e.g., page 9, lines 20-23, which reads "from 1 to 50"); the alternative reading lacks logic. In addition, Applicants have amended the claim to specify that the adenovirus "has both a VAI gene and a VAII gene." Applicants submit that this amendment remedies the alleged defects..

Finally, claim 11 has been amended to specify that the recited adenovirus is a dl331 adenovirus that further has a mutation in the VAII gene. Applicants submit that this amendment remedies the alleged defect.

For at least these reasons and in light of these amendments, Applicants submit that the claims as amended are clear and definite.

Rejections under 35 U.S.C. § 102

At page 12, claims 1 and 3 were rejected as allegedly anticipated by Little et al., USPN 6,254,862, which describes methods of treatment in which an adenovirus having a mutant Ela promoter is used to direct viral replication to cancer cells. Claim 1 recites a method including administering “an adenovirus having mutated VAI and VAII RNA genes, wherein said adenovirus is defective in its VAI and VAII virus-associated RNAs and will selectively replicate in cells of said cancer.” Little et al. does not teach or suggest mutating either VAI or VAII, let alone mutating both. Furthermore, the Office Action noted at page 12 that limiting the claims in such a manner would overcome the rejection. For at least these reasons, Applicants submit that the claims as amended are novel over Little et al.

At page 13, claims 1-3 were rejected as allegedly anticipated by Kuo et al., US Pre-Grant Pub. No. 2004/0132675. Applicants respectfully traverse. Claim 1, as amended, recites the use of an adenovirus that “will selectively replicate in cells of said cancer.” Neither the regular nor “gutless” adenoviruses used in the methods disclosed in Kuo et al. will selectively replicate in cancer cells. For at least these reasons, Applicants submit that the claims as amended are novel over Kuo et al.

Applicants thus request withdrawal of the rejection under 35 U.S.C. §102, as the pending claims are novel.

Rejections under 35 U.S.C. §103

At page 14, claim 11 was rejected as allegedly obvious over Coffey et al., WO 01/35970, in view of Thimmappaya et al., Cell, 31:543-551 (1982). Applicants respectfully traverse.

Claim 14 as amended specifies that the administered adenovirus is a dl331 further comprising a mutation in the VAII RNA gene. Neither Coffey et al. or Thimmappaya et al. suggests mutating the VAII RNA gene of the dl331 adenovirus for use in a method of treating cancer. Applicants submit that the claimed method is neither taught nor suggested by Coffey et al. or Thimmappaya et al., alone or in any combination, and request withdrawal of the rejection under 35 U.S.C. § 103.

Conclusion

Applicants submit that, for at least the reasons set forth herein, the pending claims are patentable, and request allowance thereof. If the Examiner feels that it would be useful, he is invited to telephone the undersigned at (617) 956-5985.

Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 11649-049US1.

Respectfully submitted,

Date: _____

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